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Treating pediatric port-wine stains in aesthetics

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Abstract A port-wine stain (PWS) is a vascular birthmark present in 0.3% to 0.5% of newborns. If untreated, this erythematous patch will grow proportionally with the child to thicken and darken with age. PWSs have implications for the child's quality of life for many years, with cosmetic, medical, and psychosocial disability. Controversy exists in many aspects surrounding laser treatment of these birthmarks in the pediatric population. We have reviewed the clinical features as well as the historic and current laser treatment of PWS. We have also examined the current hot topics of debate surrounding the treatment of PWS in the pediatric population. These controversies include the patient age of treatment initiation, the long-term psychologic impact, the use of general anesthesia, the application of eye shields, and alternative treatments for recalcitrant PWS. We have concluded with a discussion on the future directions of management and treatment.

Clinical features

A port-wine stain (PWS) represents a vascular malformation, which typically presents at birth as a pink-to-red patch that can occur anywhere on the body. PWSs are comprised of ectatic blood vessels of varied morphology, diameter, and depth.[1] Facial PWS can be unilateral or bilateral, commonly occurring in dermatomal or segmental patterns.[2] PWS has an incidence of 0.3% to 0.5%[2-5] without predilection for sex. Non-syndromic PWS may result from a somatic GNAQ activating mutation in vascular endothelial cells.[6] PWS will grow proportionately with the child and can become hypertrophic and nodular,[7] usually after puberty, as a result of increasing ectasia of the vessels; however, some patients have reported congenital hypertrophy or early-onset hypertrophy.[8]

The prevalence of PWS hypertrophy is debatable and has been reported as 0.4% to 65% in adults.[9-12] This not only increases the risk of spontaneous hemorrhage upon injury, but it can also be debilitating cosmetically, psychologically, and functionally.[7,9] Hypertrophic PWS on the gingiva and lips are known to create difficulties with bite or lip closure as well as bleeding.[13] PWS is usually an isolated finding, but it can also be found in various syndromes, including Sturge-Weber, Klippel Trenaunay, Proteus, and Beckwith-Wiedemann, which affect multiple organ systems and necessitate further workup and coordinated care.

Treatment of PWSs

Earlier treatment modalities

Historic treatments prior to pulsed dye laser (PDL) therapy for PWS included skin grafting, radiation therapy, der-

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mabrasion, cryosurgery, electrotherapy, tattooing, and cosmetic camouflage.[7] Because these modalities were insufficient and posttreatment scarring was common, laser intervention was considered as a potential treatment modality. The argon laser was the first laser device used for PWS, but despite effective lightening that could be achieved, adverse events were common.[14] The argon laser emits light from 458 to 514 nm at six different wavelengths and is well-absorbed by both melanin and hemoglobin[14]; however, the degree of thermal damage to the surrounding tissue causing hypertrophic scarring and hypopigmentation was unpredictable.[14]

Pulsed dye laser

PDL emerged as the preferred laser modality for PWS treatment by taking advantage of the selective photothermolysis of oxyhemoglobin in the target vessels. Initially, the 577 nm PDL was developed considering the peak absorption of oxyhemoglobin. Subsequently, longer wavelengths of 585 nm and 595 nm were developed to increase the depth of penetration, which further limits the amount of epidermal melanin absorption. Additionally, pulse duration evolved from a fixed duration of 0.45 ms to a range from 0.45 to 40 ms. A pulse duration between 1 and 10 ms approximates the vessel thermal relaxation time, which mitigates surrounding thermal injury.[15,16] PWS needs adequate, but appropriate, radiant energy to not only induce irreversible destruction of vessels, but also to avoid injuring nearby structures.[7]

The addition of dynamic cooling to the PDL device has also assisted in preventing epidermal thermal injury that can lead to scarring and dyspigmentation.[17] Additionally, dynamic cooling has been shown to offer a significant reduction in pain during treatment.[18] The PDL has seen advancements in technology with the advent of larger spot sizes, increased fluence, variable pulse width, and dynamic cooling, all of which increase efficacy by increasing target depth and vessel injury.[19]

Clinical treatment

In the authors' practice, treatment parameters for the PDL are individualized by PWS appearance and location, Fitzpatrick skin type (FST), and patient age. These parameters are also adjusted at each visit based on clinical response. With additional treatments, fluences are titrated, and with age above 1 year, we often shorten the pulse duration to 0.45 ms. The settings will vary with the device being used, and these should always be modified based on clinical response.

The clinical endpoint for PWS when using the PDL is purpura.[5] Anecdotally, we have observed that young infants do not have the same degree of purpura, and the endpoint in these patients should be a slight graying that often dissipates shortly after the pulse is delivered. For in-office treatments, topical anesthetic can be applied for patients older than 1 year of age, below which there is risk for methemoglobinemia. Common adverse effects of PDL treatment in children include transient edema, erythema, purpura, and mild postinflammatory hyperpigmentation.[20] Optimal treatment intervals for facial PWS in infants range from 2 to 4 weeks, with shorter treatment intervals leading to more rapid clearance.[20]

Fig. 1 Fitzpatrick skin type (FST) I girl with port-wine stain in V1/V2/V3 distribution, **(A)** before first treatment at 5 weeks of age and **(B)** with near complete clearance (excepting the eyebrow, which was not treated) at 10 months of age after 10 of 11 treatments.

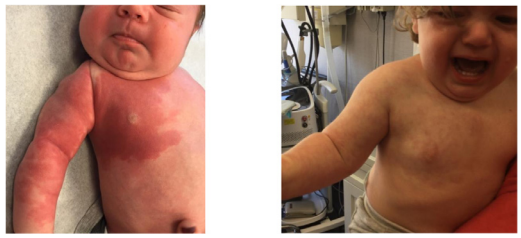

Fig. 2 Fitzpatrick skin type (FST) I boy with port-wine stain involving the chest and arm, **(A)** before first treatment at 5 weeks of age and **(B)** with significant clearance, though residual erythematous reticulation, at 19 months of age after 25 of 26 treatments.

Despite the successes of PDL for PWS treatment in children, clinical response varies with characteristics of the patient and PWS itself. Certain PWS can remain recalcitrant to therapy. Response to treatment of PWS on the face vary by location with PWS in children overlying bony prominences, such as the forehead, temple, and nose, requiring fewer treatments than those on the cheeks and lips.[21,22] When the response to laser was compared between the lateral and central face, centrofacial (medial cheek, nose, upper cutaneous lip) lesions responded less favorably.[23] The V2 dermatome responded the least.[5,23]

When treatment is initiated early, even difficult-to-treat locations can have excellent results (Figure 1). Facial PWSs larger than 40 cm^2 were found to have less clearing with PDL than lesions smaller than 20 cm^2, and this difference was independent of patient age.[24,25] PWSs on the distal aspects of the arms and legs are more difficult to treat than those located on the face.[26] Although lesions not on the face are more challenging, treatment may be optimized when begun early in life (Figure 2).

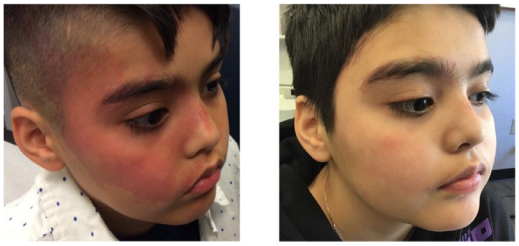

Fig. 3 Fitzpatrick skin type (FST) IV boy with port-wine stain in V1/V2 distribution, **(A)** before treatment at 9 years of age and **(B)** at 12 years of age with near complete clearance after 13 of 14 treatments.

The treatment of PWS with PDL in darker skin types, such as Hispanic, Asian, and African American skin, is especially challenging, because melanin in epidermal pigment competes with the desired chromophore, oxyhemoglobin. This increases the risk of posttreatment blistering and dyspigmentation. A recent series of 98 PWSs in skin types IV and V were treated with the 595 nm PDL with a mean lightening of 54% in flat and 40% in hypertrophic PWS.[27] The 595 nm PDL was also successfully used without adverse events in two pediatric patients of skin types IV and V, who were treated early and often.[28] PDL treatment at short intervals of 3 weeks has demonstrated safety and efficacy in East Indian patients as young as 3 months.[29] In a recent large study of infants under 1 year of age who were treated with PDL, 16 were FST IV and 2 were FST V to VI, and of these 18 darker skin patients, there were no significant complications.[5] Conservative PDL settings may be used by the experienced laser surgeon in the treatment of PWS in dark skin types with low risk of adverse events and optimal results (Figure 3).

In light of both safety profile and efficacy, the 595 nm PDL is currently the treatment of choice for PWS. Other lasers that have been successfully used for recalcitrant PWS will be discussed in detail below.

Controversies and debates with PWSs

Patient age of treatment initiation

Treatment of PWS should begin as early as possible, preferably in early infancy.[30] Since the days of treating PWS with the shorter wavelength PDL, younger children have been observed to respond better than older children. A study found that children who were 0 to 6 years of age required fewer treatments for optimal response than those aged 7 to 14 years.[21]

PDL treatment efficacy in infants younger than 1 year is superior to treatment initiated at older ages in multiple studies. In an analysis of children ranging from 2 weeks to 12 years of age who had PWS treated with PDL, children younger than 1 year had an increased rate of complete clearance compared with those who were older.[25] Another study found 63% of 16 infants under 1 year of age achieved 75% clearance of PWS in an average of 4 treatments with a high-fluence approach.[31]

Fig. 4 Fitzpatrick skin type (FST) I girl with port-wine stain in V2/V3 distribution, **(A)** before first treatment at 1 month of age and **(B)** with near complete clearance at 20 months after 18 of 20 treatments.

Treatment of PWS beginning in early infancy (age 6-30 weeks) requires fewer total treatments to achieve the same outcome when compared with older children.[31-33] A study of 49 infants who began PDL treatment of their PWS under 6 months of age included infants as young as 2 to 3 weeks old. Not only could the infants at this age be treated safely, but also these infants demonstrated on average 91% of the lesion cleared after 9 treatments.[30]

The reasons as to why younger patients respond better to laser treatment have been theorized. Younger patients have vessels that are smaller in diameter, are less full of red blood cells, and cover a smaller area of the dermis.[34] PWSs grow proportionately with the child, and thus, the surface area is smallest in infancy, which can allow for more rapid treatment. In addition, skin thickness increases with age resulting in vessels lying deeper in the dermis, which can cause scattering of the laser beam. The thinner skin of infancy allows for better laser penetration.[35]

Punch biopsies before laser treatment have been performed in adults to correlate the histology with treatment response, showing poor responders having deeper vessels.[36] Laser fluence decreases with increasing penetration depth.[30] As children become older, the larger and more developed blood vessels with thicker skin may produce multiple barriers to efficient selective photothermolysis targeting the blood vessels. When initiated early and aggressively, albeit safely, PDL treatment of PWS has the greatest chance for rapid and complete clearance (Figure 4). Because early treatment increases the ultimate degree of clearance, this can help to prevent nodular and hypertrophic progression of the PWS later in life.

Long-term psychologic impact

Patients with PWS experience decreased quality of life with greater psychosocial stress and morbidity. This can have implications for the patient and their family. A large survey study of 244 adults with PWS revealed reduced quality of life, largely from an emotional standpoint, and especially so in those with hypertrophy.[37] A questionnaire study of 71 pa-

tients who were at least 15 years of age revealed a high level of psychological distress resulting from feelings of stigmatization and difficulties with interpersonal relationships.[38] Another study of 76 adults with PWS receiving laser treatment found higher emotional stress and impairment in social life with lower perceptions of self-attractiveness when compared with a control group without PWS.[39]

The patients with greater emotional stress had elevated expectations for quality of life after laser therapy. A questionnaire of patients from 2 to 74 years of age that focused on psychosocial impact found that older patients had worse scores than younger patients,[40] which supports the clinical benefit of early treatment. Eighty percent of the surveyed patients over 7 years of age had still not accepted their PWS and believed that removal would improve their life. Importantly, studies have demonstrated that patients who have had their PWS treated have improvement in quality of life, especially the psychosocial functions of self-esteem and social interactions.[9,40,41]

General anesthesia

In 2017, the US Food and Drug Administration issued a new warning that exposure to general anesthesia under the age of 3 years, either for multiple procedures or for prolonged length of time, may have a negative impact on brain development.[42] Despite this, impassioned debate remains over the use of general anesthesia in the pediatric population for elective procedures. This is especially relevant in the treatment of PWS, which requires numerous treatments in short intervals for optimal results.

It is crucial to first evaluate the potential harm to an infant when undergoing general anesthesia at a young age. Multiple studies have revealed the association between the repetitive use of general anesthesia under the age of 3 years and neurocognitive impairment.[43-46] The risk of neurocognitive impairment has also been demonstrated in older children with chronic conditions subject to high cumulative exposure to anesthesia.[47]

The other arm of the debate raises the concern of risk posed to the infant of undergoing painful procedures without general anesthesia. Studies have demonstrated that neonates and infants do perceive pain, and those who experience pain during infancy, for example in neonatal circumcisions without anesthesia, may have short-term changes in sleep and behavior on the order of hours to days.[48]

There is concern that infants, especially premature infants who are highly vulnerable, who undergo pain repeatedly or in a prolonged manner can experience short-term stress, which may have long-term neurodevelopmental effects, and changes in future pain perception[49]; however, the theory that pain in infancy has long-lasting memory and subsequent long-term effects has limited human data.[48,49] Additionally, in the question of pain experienced during procedures, the type of procedure and extent of pain should be considered. It is not justifiable to compare the pain of surgical procedures, such as heel cord lengthening, to PDL without anesthesia.[50,51]

PDL is not a pain-free procedure; nevertheless, pain may be reduced significantly by dynamic cooling.[18] A large retrospective study of infants under 1 year of age with PWS found that PDL treatment in the office without the use of general anesthesia was both safe and effective.[5] The authors presume that the discomfort experienced by the infants is temporary and mild, because their crying subsides by the time they leave the treatment room and in most cases, within seconds to minutes after treatment.[51]

Other benefits of starting the treatment in younger infants without general anesthesia are ease of restraining a smaller child[5] and possibly limited memory of the events if treatments are completed in infancy. In our experience, older infants and toddlers appear to recall pain associated with the PDL treatment, because some of them cry when brought into the treatment room, which is not evident in younger infants. The authors strongly believe that the benefits to the infant of early treatment without exposure to general anesthesia far outweigh the risks. Our beliefs are further substantiated by the parents who bring their children back for these repeated treatments.[51]

Eye shields

Another debate in the literature is whether to use corneal eye shields in infants. These shields are protective lenses that are placed directly on the eye before procedures that involve the periocular region.[5,52,53] Although guidelines do not exist for their use, studies have demonstrated the importance of metallic over plastic shields in laser surgery owing to potential for corneal thermal damage seen with the latter.[54] For laser treatment of PWS involving the periocular region, metal eye shields of appropriate size can safely be placed in patients after application of topical anesthetic ophthalmic drops.[5,52]

Anecdotally, among the community of dermatologists who treat pediatric patients with periocular PWS, a select few feel comfortable placing corneal eye shields. Fewer yet will do so in patients under 6 weeks of age and/or in patients who are not under general anesthesia. In our practice, based on the literature and our experience, we treat early and frequently regardless of PWS location, and we place eye shields when necessary to obtain optimal outcomes as early as possible without the use of general anesthesia. We have found this approach to be safe and effective.[5]

Alternative treatments for pediatric PWS recalcitrant to PDL

Despite the logistical challenges in the treatment of PWS in the pediatric population, and the optimization of results when treatment is initiated early, complete clearance is never guaranteed. Alternative treatments to PDL exist, but available data are limited.

Once response is plateauing despite multiple PDL treatments, another energy-based therapy can be considered in

a child. Unfortunately, all alternative options have an increased potential for adverse events, and their lack of high-quality data, especially in the pediatric population, compels laser surgeons to rely on personal experience. Additional devices include the 532 nm potassium titanyl phosphate (KTP) laser, 755 nm Alexandrite laser, 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, and combination PDL-radiofrequency (RF) device.

The 532 nm wavelength of KTP is close to the oxygenated hemoglobin absorption peak, which provides a rationale for its use in blood vessel treatment. The efficacy of the KTP laser in treating PWS recalcitrant to the PDL was studied.[55] Out of 30 patients enrolled, three were under the age of 18 of which two had over 25% lightening and none had resultant scarring or hyperpigmentation. Another study that showed efficacy of the KTP for PWS resistant to PDL did not include pediatric patients.[56] Epidermal injury is not uncommon because the 532 nm wavelength is close to the melanin absorption peak. The penetration of KTP is also shallower than PDL, which makes it a less attractive choice for residual deeper vessels. The small spot size can be limiting in the treatment of large PWS.

The longer wavelength of the 1064 nm Nd:YAG and 755 nm Alexandrite lasers allow for deeper penetration, which offer advantage with deeper vessels. The Nd:YAG also has decreased risk of postinflammatory hyperpigmentation in darker skin types; however, these lasers require delivery of higher energy to damage the vessels, which increases the risk of serious adverse events of scarring.[57] The 755 nm Alexandrite is better absorbed by deoxyhemoglobin than oxyhemoglobin and thus, is suitable for targeting capillaries and postcapillary venules that are malformed in PWS. A retrospective review of 13 children with facial PWS resistant to PDL, who were 5 months to 16 years old, were treated with Alexandrite and/or PDL with mild-to-moderate lightening in all cases but one.[58] There was one case of scarring and another with blistering. The risk of scarring with the Alexandrite in adults appears to be greater than the 0% to 4.3% risk associated with the PDL, which is likely owing to deeper tissue penetration.[59-61]

The penetration depth of the Nd:YAG laser is 4 to 5 mm compared with the 1 to 2 mm of PDL, which provides an advantage in targeting deeper vessels. As part of a larger study of children and adults, 16 PWS patients under 18 years of age were treated with combined 595 nm PDL and 1064nm Nd:YAG laser.[62] This strategy takes advantage of the shift of hemoglobin to methemoglobin after irradiation with the 595 nm PDL. Methemoglobin absorbs 1064 nm more efficiently than hemoglobin, so lower fluence can be used for comparable outcomes with fewer adverse effects. In this study, no adverse event was reported in the treated children. A report of 17 PWS in patients of FST I to IV demonstrated over 75% improvement in vascular blebs after a single treatment using 1064 nm Nd:YAG laser with contact cooling without any adverse events.[57] Although vascular blebs are not often seen in the pediatric population, anecdotally, the authors will use the 1064 nm Nd:YAG laser to treat vascular blebs in conjunction with PDL treatment of the entire PWS.

A combination PDL-RF device has been discussed.[63] The theory for its use in recalcitrant PWS is that heat production from PDL alone may be inadequate to destroy larger blood vessels. A small open-label investigation of 10 patients with 11 recalcitrant PWSs underwent a maximum of six treatments divided into five areas (PDL alone, RF alone, PDL+RF, RF+PDL, and untreated control).[63] The study found a significant improvement at 12 weeks in the areas treated with combination PDL+RF and RF+PDL compared with either monotherapy.[63] One scar occurred in one patient; otherwise, adverse events were largely anticipated and transient, which included edema, erythema, purpura, and scabbing/blistering. The authors have this device and typically reserve it for use in adult patients.

Future directions

The younger the patient with PWS, the better the anticipated response to laser therapy; however, treatments initiated during infancy do not guarantee complete clinical clearance. Wound healing after laser therapy leads to angiogenesis, which makes complete clearance more challenging.[64] Emerging therapies for pediatric PWS include photodynamic therapy (PDT) with a photosensitizer specifically targeting blood vessels and laser-assisted drug delivery (LADD) of topical angiogenesis inhibitors. With newer devices on the horizon, there is also the potential for enhanced laser capacity with minimization of adverse events.

Hematoporphyrin monomethyl ether

Hematoporphyrin monomethyl ether (HMME) is a porphyrin-related photosensitizer. In 2016, it was approved in China for treatment of PWS. HMME is transfused intravenously, and its uptake by vascular endothelial cells allows for concentration within PWS. In a reaction with HMME and 532 nm green light-emitting diode, reactive oxygen species and phototoxic particles are created, which subsequently damage the targeted blood vessels without epidermal injury.[65] The efficacy and safety profile of HMME-PDT for pediatric PWS has been evaluated in Chinese patients. In a small study of 10 patients under the age of 18, treatment with HMME-PDT had a response rate of 87% with most experiencing short-term erythema, whereas a few also had temporary hyperpigmentation and crusting.[65]

In a larger study, 82 patients between 1 to 14 years of age were treated twice with HMME-PDT. Of all responses, there was a 30% cure rate, 41% with good efficacy, 20% with alleviation, and only 10% with no efficacy.[66] The treatment was generally tolerated with burning sensation and pain; however, there were 22 cases of dyspigmentation and 22 cases of crusting. In a study of over 100 children between 1 to 3 years of age, HMME-PDT treatment was associated with a 98% effective rate (defined as partial depigmentation in the

treatment area with degree of improvement ≥20%).[67] The most common adverse effects were itching and edema, and two patients developed scars. No serious systemic adverse events were reported in either study, including in young children.[66,67]

Topical agents

Topical agents as monotherapy have had mixed results in the treatment of pediatric PWS. Topical timolol, a beta-blocker effective in the treatment of infantile hemangioma, is thought to potentially inhibit angiogenesis by blocking the vascular endothelial growth factor pathway.[68] In a multicenter randomized controlled trial with 22 children, efficacy of combination therapy with PDL and topical timolol did not show improved results compared with PDL alone.[69]

Imiquimod prevents neovascularization by induction of antiangiogenic cytokines, expression of endogenous angiogenesis inhibitors, and endothelial apoptosis.[70] In small pilot and feasibility studies, combination PDL treatment with adjunctive posttreatment topical imiquimod demonstrated greater blanching response compared with either PDL or imiquimod alone.[71,72]

Laser-assisted drug delivery

LADD of angiogenesis inhibitors has the potential to enhance drug uptake and subsequently improve efficacy. LADD involves pretreatment of the affected area with laser to cause selective epidermal and dermal destruction allowing for increased penetration of topical medications.[73] Rapamycin, a mammalian target of rapamycin pathway inhibitor that downregulates hypoxia-inducible factor synthesis and regulates vascular endothelial growth factor expression, may hold promise in conjunction with LADD.

Animal studies have shown that topical rapamycin applied after PDL inhibited protein expression of HIF-1a and vascular endothelial growth factor and reduced vessel formation and perfusion.[64,74] Small clinical trials have shown equivocal efficacy of combined treatment of PDL and topical rapamycin, compared with PDL alone.[75-77] LADD to improve penetration efficiency of topical rapamycin is being investigated. In addition to a fractional ablative laser, a non-laser thermomechanical system, called Tixel (Netanya, Israel), is under investigation, and induces desiccation of the epidermis to create channels through the epidermis into the dermis.[78] Future research should be performed to investigate the added benefits of LADD with rapamycin to PWS in conjunction with PDL.

Optical coherence tomography

Optical coherence tomography is a noninvasive imaging device that can efficiently provide blood vessel depth and diameter in vascular lesions.[1] This knowledge can enhance the selection of fluence to better match vascular depth, as well as pulse duration to better match thermal relaxation time, which is based on vessel diameter.[79] Using optical coherence tomography, PWSs were found to be comprised of vessels of varied morphology, diameter, and depth, which contribute to the challenge of treating these lesions.[1] Use of this imaging modality can allow for more targeted selection of PDL parameters and the potential for enhanced PWS clearance in fewer treatments.[79]

Conclusions

PWS are challenging lesions for patients to live with and for physicians to treat. Complete clearance is difficult to achieve; however, treatment is most successful when the 595 nm PDL is initiated in early infancy and performed frequently, because this has the greatest chance for ultimate clearance in the most rapid manner. Treatment of PWS early on mitigates future risk of nodularity and hypertrophy, as well as reduces risk for psychosocial distress and decreased quality of life. A multitude of controversial topics surrounding the treatment of PWS exist. Although many PWS become recalcitrant to PDL, current technologies can improve treatment of these lesions, and future advances are underway.

Conflict of interest

Margo H. Lederhandler and Hyemin Pomerantz—subinvestigator for Lutronic, Candela; David Orbuch—none; Roy G. Geronemus—Medical Advisory Board for Allergan, Candela, Cearna, Cynosure, Cytrellis, Lutronic, Novoxel, Soliton; Investigator for Allergan, ArchiMedus, Avava, Candela, Cherry Imaging, Cynosure, Cytrellis, Endo Pharmaceuticals, Galderma, Kerastem, Lutronic, Merz, Michelson Diagnostics LTD, New York Stem Cell Foundation, Pulse Biosystem, Revance, Sciton, Quanta Accure; Stockholder for Cytrellis.

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